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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/436,265	10/30/95	MIYAZONO K.	LUD-5298-JEL

EXAMINER

18N2/0709

FITZGERALD, D.

ART UNIT	PAPER NUMBER
1812	20

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DATE MAILED: 07/09/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 28 April 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire — THREE — * month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a). * NOTE the one-month time limit to copy claims suggested at ¶ 1 infra. This one-month time limit CANNOT be extended.

Disposition of Claims

☒ Claim(s) 1-29 is/are pending in the application.
Of the above, claim(s) 20 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-19, 21-29 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-29 are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496

1. The following allowable claims are suggested for the purposes of two distinct interferences.

A1. An isolated nucleic acid molecule encoding an ALK-3 polypeptide comprising the amino acid sequence of murine ALK-3 as shown in SEQ ID NO: 14 or the sequence of human ALK-3 as shown in SEQ ID NO: 6.

A2. An isolated and purified ALK-3 polypeptide comprising the amino acid sequence of murine ALK-3 as shown in SEQ ID NO: 14 or the sequence of human ALK-3 as shown in SEQ ID NO: 6.

B1. An isolated nucleic acid molecule encoding an ALK-6 polypeptide comprising the amino acid sequence of murine ALK-6 as shown in SEQ ID NO: 18.

B2. An isolated and purified ALK-6 polypeptide comprising the amino acid sequence of murine ALK-6 as shown in SEQ ID NO: 18.

The suggested claims must be copied exactly, although other claims may be proposed under 37 C.F.R. § 1.605(a).

Claims 21-29 as they now appear are considered unpatentable over either one of suggested claims A1 or B1. Claims 1-19 as they now appear are considered unpatentable over either one of suggested claims A2 or B2.

Applicant should present the suggested claims within ONE MONTH or THIRTY DAYS from the date of this letter, whichever is longer. Under the provisions of 37 C.F.R. § 1.605(a), the failure to do so will be considered a disclaimer of the subject matter of the claims not copied. THE PROVISIONS OF 37 C.F.R. § 1.136(a) DO NOT APPLY TO THIS TIME PERIOD.

2. Applicant's election with traverse of Group I, claims 1-19 and 21-29, in the response filed 14 April 1997 (Paper No. 19) is acknowledged. The traversal is on the ground(s) that claim 20 is "linked" to the invention of group I by virtue of its dependence from claim 1. This argument is not persuasive because unity of invention is determined without regard to the manner in which the inventions are claimed. PCT Rule 13.3.

Claim 20 stands withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected invention(s).

3. Upon further review of the disclosure, claims, and prior art, the examiner considers that further restriction with respect to the elected invention is appropriate. Accordingly,

restriction to one of the following inventions is required under 35 U.S.C. §§ 121 and 372 and 37 C.F.R. § 1.499:

I. A protein meeting any of the alternative limitations of claim 1 and a nucleic acid encoding it.

II. An ALK-1 protein and a nucleic acid encoding it (exemplified by SEQ ID NOs: 1, 2, 11, and 12).

III. An ALK-2 protein and a nucleic acid encoding it (SEQ ID NOs: 3 and 4).

IV. An ALK-3 protein and a nucleic acid encoding it (SEQ ID NOs: 5, 6, 13, and 14).

V. An ALK-4 protein and a nucleic acid encoding it (SEQ ID NOs: 7, 8, 15, and 16).

VI. An ALK-5 protein and a nucleic acid encoding it (SEQ ID NOs: 9 and 10).

VII. An ALK-6 protein and a nucleic acid encoding it (SEQ ID NOs: 17 and 18).

Because the limitations of even the most narrow claims are met by a protein having "all or part" of the various peptide sequences specified, *e.g.*, single amino acid residues, all of claims 1-19 and 21-29 are readable on all of the inventions as set forth above.

Because this application was filed under 35 U.S.C. § 371, the PCT Unity of Invention standard is applicable to the instant claims. 37 C.F.R. § 1.499.

Claim 1 sets forth as one of its alternative limitations "having a serine/threonine kinase domain corresponding to that in daf-1 . . . ." Accordingly, the daf-1 gene product, which is admitted in the instant disclosure to belong to the prior art, satisfies the limitations of the claim. Because the generic invention of claim 1 is not novel, it does not constitute a special technical feature within the meaning of PCT Rule 13.2 which defines an advance over the prior art. Accordingly, none of the inventions corresponding to the products ALK-1, -2, -3, -4, -5, and -6 is so linked to the invention of Group I as to form a single general concept within the meaning of PCT Rule 13.1. Furthermore, pursuant to 37 C.F.R. § 1.475(d), the DO/US considers that all of the aforementioned ALK products do not correspond to the main invention of Group I. Restriction for examination purposes as indicated is accordingly proper.

During a telephone conversation on 24 June 1997, Vineet Kohli made a provisional election with traverse to prosecute the invention of group VI, ALK-5 proteins and nucleic acids,

upon which all of claims 1-19 and 21-29 are readable. Affirmation of this election must be made by applicant in responding to this Office action.

Notwithstanding that the several inventions lack unity within the meaning of PCT Rule 13.1 as set forth above, the examiner is withdrawing the restriction requirement in part to permit examination of the subject matter corresponding to the claims suggested for interferences above. Accordingly, claims 1-19 and 21-29 will be examined with respect to ALK-5, as provisionally elected by applicant, and also ALK-3 and ALK-6.

4. This application was filed under the provisions of 35 U.S.C. § 371. The examiner has reviewed and considered the International Search Report (PCT/ISA/210) and the International Preliminary Examination Report (PCT/IPEA/409) prepared during the international stage of this application. Additionally, all of the references cited in the Search Report, some of which applicant has also cited in an Information Disclosure Statement, have been considered.

5. The abstract is objected to under 37 C.F.R. § 1.72(b) because extraneous material appears on the sheet containing it. (The abstract filed with the application is the PCT publication "cover sheet.") Deletion of the current abstract page and submission of an abstract on a separate sheet are required.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required: the specification does not describe a "GS box" as a feature of the receptors of the invention.

7. Claim 2 is objected to under 37 C.F.R. § 1.821(d) for failing to recite a sequence identifier (*i.e.*, a SEQ ID NO) concurrently with the recited sequence. Note that if the consensus ATP-binding sequence recited in the claim cannot be described with reference to any of the sequences in the Sequence Listing, a substitute Sequence Listing will be required.

8. Claims 21 and 25 are objected to under 37 C.F.R. § 1.75(b) as being duplicate claims. The claims appear to be identical in scope and content because the recited alternatives in dependent claim 25, DNA and RNA, exhaust the possibilities for nucleic acid molecules according to claim 21. One of the duplicate claims should be canceled or otherwise amended to delimit a different scope of the invention. Applicant's attention is also directed to M.P.E.P. § 706.03(k).

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 19 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 19 cannot be practiced because it requires mutually exclusive limitations. Claim 1, from which the claim depends, requires the presence of "a receptor serine/threonine kinase domain," *i.e.*, a substantial intracellular domain. Claim 19, on the other hand, is directed to a "soluble receptor." As the term is employed in the specification and understood in the art, a "soluble receptor" is a polypeptide corresponding to the extracellular domain of a receptor, lacking the transmembrane and intracellular domains of the native receptor. The claim therefore requires conflicting limitations which cannot be simultaneously incorporated in any single embodiment.

11. Claims 1-18 and 21-29 are rejected under 35 U.S.C. § 112, first paragraph. The specification is enabling for mammalian ALK-3, -5, and -6 cDNAs which can be retrieved using the disclosed sequences as probes, their translation products, and polypeptide sequences differing from them by a small number of amino acid substitutions. However, it does not reasonably provide enablement for nucleic acids or proteins having only the minimal structural components common to the disclosed ALK sequences. Furthermore, the specification does not teach how to make "hosts" other than cultured host cells. Finally, the specification does not teach how to make the Chim A receptor plasmid required to practice the invention of claim 29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention in a manner which is commensurate in scope with the claims.

Scope of ALK products supported

The disclosure does not teach how to use the full scope of receptor proteins having only the minimal structural features characteristic of the kinase domains of the disclosed ALK clones, partial structures of the disclosed sequences or other TGF-β or activin receptors, or proteins having only 60% or lower identity to the disclosed sequences. All of the disclosed uses for the receptor proteins ultimately depend upon their functional properties, *i.e.*, the ability to bind specifically to ligands, associate with Type II receptors, and to transduce signals in response to ligand binding. The disclosure does not teach how to modify any of the disclosed sequences in a manner which would predictably retain or confer any particular desired functional properties.

In order to make a sequence variant of any of the disclosed receptors with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed molecule are responsible for the interactions underlying its biological function(s). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed.

For receptor sequences having one or two substitutions relative to those disclosed, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases, the number of possible variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. For

the reasons discussed above, such experimentation would be undue for one skilled in this art. See, for example, *Amgen v. Chugai,* 18 USPQ2d 1016 (Fed. Cir. 1991); *Ex parte Maizel,* 27 USPQ2d 1662 (BPAI 1993).

The disclosure does not teach how to make any protein having a "GS Box" because this feature is not described or discussed in the application. It cannot even be ascertained from the disclosure whether any of the ALK products particularly disclosed has this feature. Absent knowledge of what constitutes a "GS Box" as contemplated by applicant, it would require undue experimentation of the skilled artisan to make receptor proteins having one.

Scope of "hosts" supported

The specification does not teach how to make or use a "host" as recited in claims 27-29 other than a cultured host cell. The recited term reads broadly on transgenic animals, including humans. Only cultured host cells are discussed din the specification. No teachings are provided which would permit the artisan to reproducibly prepare a transgenic animal, for example, expressing an ALK receptor in specific tissues or in all its tissues. Furthermore, the uses disclosed for the intact hosts of the invention require that they express defined populations of TGF-β superfamily receptors. The disclosure does not teach how to control the endogenous receptor populations expressed by various animal tissues. It would accordingly require undue experimentation of the skilled artisan to practice the full scope of the invention with respect to arbitrary "hosts" as required by claims 27-29. Amendment of the claims to recite "cultured host cell(s)" would obviate this ground of rejection.

Chim A plasmid

The specification does not provide a repeatable method for obtaining the Chim A plasmid, and it does not appear to be a readily available material. At page 33, the specification describes the translation product encoded by the plasmid, but it does not describe the plasmid *per se* in any detail. Access to the Chim A plasmid *identically* is required to practice the invention of claim 29. Absent a complete description of the plasmid or a repeatable method of making it, it would require undue experimentation of the skilled artisan to practice the invention as claimed. Deposit of the plasmid in a suitable host cell would satisfy the enablement requirements of 35 U.S.C. § 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating

(a) that the deposit has been made under the terms of the Budapest Treaty; **and**

(b) that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent,

would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then the requirements may be satisfied by an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or by a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and establishing that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807 is provided; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function described in the manner in the specification.

In either case, the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification if it is not already present. See 37 C.F.R. §§ 1.803-1.809 for additional explanation of these requirements.

12. Claims 1-19 and 21-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and the claims dependent therefrom are vague and indefinite with respect to the recitation of "and/or" because it is not clear which combination(s) of the recited alternatives are required to define the subject matter of the claim. (For the purposes of applying the prior art, the claims have been interpreted as being satisfied by any of the recited alternatives.)

Claims 3, 7, 8, and the claims which depend from them are vague and indefinite because the specification does not describe or employ in context the term "GS box." It therefore cannot be determined what structural features are required to satisfy the limitations of the claims, the metes and bounds of which are accordingly indefinite.

Claims 6, 8, and the claims dependent therefrom are vague and indefinite because it is not clear what constitutes activin or TGF-β type I receptor "functionality." The term could be reasonably employed to require, for example, all of the functional properties of native type I receptors or, alternatively, only some of the properties, such as ligand binding.

Claims 7, 9, and the claims which depend from them are confusing and indefinite because it is not clear whether any relationship is required between the recited "type II receptor interaction" and "[ligand]-binding activity." It is not clear, for example, whether a receptor polypeptide which bound ligand independently of its ability to interact with a type II receptor would be within the bounds of the claims.

Claim 22 is confusing, incomplete. and indefinite for failing to recite the defining characteristics of the second required heterologous sequence.

Claim 25 is incomplete and indefinite because the claim from which it depends recites no antecedent either for "DNA [molecule]" or "RNA/mRNA [molecule]." It is additionally vague and indefinite because it is not clear whether an RNA molecule which is not mRNA would fall within the bounds of the claim.

Claim 26 and the claims dependent therefrom are confusing and incomplete as they appear to require the functional characteristics of nucleic acids but depend from a claim directed to an antibody, lacking any antecedent for the recitation of "the coding sequence." They are additionally vague and indefinite for failing to indicate an unambiguous antecedent for "the protein," as plural proteins are identified in base claim 20.

Claim 27 and dependent claims 28-29 are vague and indefinite because it is not clear whether it is the "host" or the "molecule according to claim 26" which must meet the limitation of being capable of expressing the protein.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 2, 21, and 22 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over the sequence of a cDNA encoding the daf-1 gene product, which applicant indicates was publicly known more than one year prior to the filing of the instant application (see specification at page 3, lines 12-15).

The daf-1 sequence appears to meet one of the alternative limitations of claim 1 inasmuch as it necessarily has its own kinase domain. Moreover, as shown in instant Fig. 1, the daf-1 protein inherently comprises the GXGXXG ATP-binding motif. The disclosure of the cDNA in the prior art conveys the preparation of nucleic acid molecules comprising "two heterologous sequences" inasmuch as cDNAs are necessarily made and propagated in chimeric vectors. To the extent that the prior art does not disclose proteins or nucleic acids meeting the purity limitations of the claims, it would have been obvious to isolate such products in order to use them, *e.g.*, for sequencing or for the preparation of antibodies, as was known generally in the art.

15. Claims 1-18 and 21-25 are rejected under 35 U.S.C. § 102(e) as being anticipated by Donahoe *et al.* (U.S. Patent No. 5,538,892).

Donahoe discloses a cDNA, denominated *misr4*, which encodes a rat TGF-β type I receptor protein, as well as vectors and host cells comprising the *misr4* cDNA insert. Heterologous expression of the receptor polypeptide is also disclosed (abstract). The Donahoe

patent claims nucleic acids encoding the MISR4 gene product (SEQ ID NO: 17) and related mammalian TGF-β receptor polypeptides. MISR4 exhibits a high degree of identity to the ALK-5 amino acid sequence shown in instant SEQ ID NO: 10; the predicted intracellular domain sequences, which necessarily comprise the complete kinase domains, are identical. A comparison of the sequences is set forth below (Db = Donahoe SEQ ID NO: 17; Qy = instant SEQ ID NO: 10).

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  Query Match           93.7%;  Score 3454;  DB 5;  Length 501;
  Best Local Similarity 95.3%;  Pred. No. 1.88e-288;
  Matches   483;  Conservative    5;  Mismatches   9;  Indels  10;  Gaps   4;

Db       1 MEAASAALRRCLLLIVLVAAAT----LLPGAKALQCFCHLCTKDNFTCETDGLCFVSVTE 56
           |||| || |  |||:|| |||:    ||||| |||||||||||||| ||||||||||
Qy       1 MEAAVAAPRPRLLLLVLAAAAAAAAALLPGATALQCFCHLCTKDNFTCVTDGLCFVSVTE 60

Db      57 TTDKVIHNSMCIAEIDLIPRDRPFVCAPSSKTGAVT--YCCNQDHCNKIELPTTGPFSEK 114
           |||||||||||||||||||||||||||||||:||  ||||||||||||||     |
Qy      61 TTDKVIHNSMCIAEIDLIPRDRPFVCAPSSKTGSVTTTYCCNQDHCNKIELPTT---V-K 116

Db     115 QSAGLGPVELAAVIAGPVCFVCIALMLMVYICHNRTVIHHRVPNEEDPSLDRPFISEGTT 174
            |:||||||||||||||||||:||||||||||||||||||||||||||||||||||||||
Qy     117 SSPGLGPVELAAVIAGPVCFVCISLMLMVYICHNRTVIHHRVPNEEDPSLDRPFISEGTT 176

Db     175 LKDLIYDMTTSGSGSGLPLLVQRTIARTIVLQESIGKGRFGEVWRGKWRGEEVAVKIFSS 234
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     177 LKDLIYDMTTSGSGSGLPLLVQRTIARTIVLQESIGKGRFGEVWRGKWRGEEVAVKIFSS 236

Db     235 REERSWFREAEIYQTVMLRHENILGFIAADNKDNGTWTQLWLVSDYHEHGSLFDYLNRYT 294
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     237 REERSWFREAEIYQTVMLRHENILGFIAADNKDNGTWTQLWLVSDYHEHGSLFDYLNRYT 296

Db     295 VTVEGMIKLALSTASGLAHLHMEIVGTQGKPAIAHRDLKSKNILVKKNGTCCIADLGLAV 354
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     297 VTVEGMIKLALSTASGLAHLHMEIVGTQGKPAIAHRDLKSKNILVKKNGTCCIADLGLAV 356

Db     355 RHDSATDTIDIAPNHRVGTKRYMAPEVLDDSINMKHFESFKRADIYAMGLVFWEIARRCS 414
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     357 RHDSATDTIDIAPNHRVGTKRYMAPEVLDDSINMKHFESFKRADIYAMGLVFWEIARRCS 416

Db     415 IGGIHEDYQLPYYDLVPSDPSVEEMRKVVCEQKLRPNIPNRWQSCEALRVMAKIMRECWY 474
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     417 IGGIHEDYQLPYYDLVPSDPSVEEMRKVVCEQKLRPNIPNRWQSCEALRVMAKIMRECWY 476

Db     475 ANGAARLTALRIKKTLSQLSQQEGIKM 501
           ||||||||||||||||||||||||||
Qy     477 ANGAARLTALRIKKTLSQLSQQEGIKM 503
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The prior art polypeptide, cDNA, and vectors manifestly meet the limitations of claims 1, 2, 9, 21-23, and 25. Because the prior art amino acid sequence comprises amino acid residues which are present in all of the disclosed ALK polypeptide sequences, the prior art protein necessarily meets the limitations of all of claims 10-18 as well. (Detectably larger regions of sequence identity with respect to all of the ALK sequences are present as well.)

Because it is not clear what constitutes a GS box, it cannot be ascertained unambiguously whether the MISR4 protein possesses one. However, in view of the high degree of identity between that protein and the instant ALK-5 polypeptide, which presumably has such feature, it reasonably appears that MISR4 must have a GS box as an inherent feature, absent evidence to the contrary. The prior art product therefore reasonably appears to meet all of the limitations of claims 3-8 also.

Finally, Donahoe is silent with respect to the activin-binding capability of MISR4. However, as is now known in the art, the type I receptors of the TGF-β superfamily typically exhibit a spectrum of ligand-binding activities, most receptors being capable of binding to several related ligands. In view of this knowledge and given the instant disclosure that ALK-5, which as shown above is very closely related in structure to MISR4, binds to both activin and TGF-β, it reasonably appears that the prior art receptor product is likely to inherently possess the capability of functioning as a type I receptor for activin, absent any evidence to the contrary. The limitations of claim 24 are accordingly satisfied as well.

16. No art is applied to claim 19 because, as discussed above in connection with the rejection under 35 U.S.C. § 112, first paragraph, its limitations are mutually exclusive. It is noted that Donahoe teaches the desirability of producing soluble MISR4 polypeptides (abstract).

No art is applied against claims 26-29 because it would not have been obvious to make any embodiment meeting their limitations, *viz.*, an antibody according to claim 20 adapted for expression of "the protein" or a cell comprising the same. With regard to what is presumably the intended subject matter of the claims, the examiner notes that Donahoe teaches the desirability of constructing expression vectors comprising the *misr4* insert and transforming suitable host cells therewith. It is also noted that the Chim A plasmid is disclosed to be a hybrid between receptors

whose complete sequences were known in the prior art (see page 33), and the construction of bifunctional chimeric receptors was also known in the art at the time of the invention.

The sequences of the disclosed ALK-3 and ALK-6 clones *per se* are free of the prior art.

17. The art cited but not relied upon is considered pertinent to applicant's disclosure. Ibañez *et al.* (U.S. Patent No. 5,614,609) discloses and claims a recombinant Ser/Thr kinase receptor polypeptide denominated ALK-7. Pacifici *et al.* (U.S. Patent No. 5,521,295) evidences that the methodology and utility of making chimeric receptors by "domain swapping" was known in the art at the time of the instant invention; see generally the prior art discussed at cols. 3-4.

18. No claim is allowed.

19. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934
Fax - Art Unit 1812	(703) 308-0294
e-mail	david.fitzgerald@uspto.gov

Inquiries of a general nature should be directed to the Chemical Matrix receptionists at (703) 308-0196.

DAVID L. FITZGERALD
PRIMARY EXAMINER
ART UNIT 1812

6 July 1997

Examiner Fitzgerald is generally available weekdays from 8 a.m. to 4 p.m. (Eastern). If he is not available to take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the supervisor for Art Unit 1812, Stephen Walsh, may be reached at (703) 308-2957.

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Most official papers and all informal communications may be submitted to the PTO by fax. For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30.

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